Applicants respectfully traverse the Examiner's restriction requirement for the reasons stated in Applicants' Responses To Restriction Requirement (Paper Nos. 8 and 10), which are incorporated herein by reference, and reserve the right to petition the Commissioner regarding the requirement for restriction.

The Rejection of Claims 28-39 and 43-44 for Lack of Enablement Is Improper Because The Examiner Has Not Established A Prima Facie Case Of Non-Enablement

The Examiner rejected claims 28-39 and 43-44[1] under 35 U.S.C. § 112, first paragraph, because the specification "does not reasonably provide enablement for the method as claimed in any and all cells in a host **(in-vivo)** using all viral or non-viral vectors." (Office Action at page 3) (additional emphasis added). For the reasons that follow, Applicants respectfully traverse this rejection.

At pages 3-4 of the Office Action the Examiner briefly summarizes Applicants' enabled invention, that is, the making and using of single-chain antibodies that bind to mutated p53 protein (or nucleic acids encoding the antibodies) to successfully restore the transactivating function or cell growth regulation in proliferating cells. Applicants, at numerous places in the specification, explain how and why the claimed invention is enabled. For example, page 1, lines 9-21, describes the "novel molecules" of the invention as useful in vitro, ex vivo, and in vivo for restoring p53 activity in tumor cells. Without limiting the scope to any particular mechanism, Applicants further explain the antibody-binding action on p53 and, more specifically, on mutated p53 (page 7, line 12 through page 8, line 19). In addition, Applicants state how the single-chain antibodies can act within a cell (page 8, line 27 through page 9, line 27), and how libraries of antibodies corresponding to the single-chain antibodies can be constructed, transferred to cells,

[1] Applicants request clarification of the status of claims 40-42, which are not listed among the rejected claims in the Examiner's remarks, but which have been included in the

and used in vivo to restore p53 transactivation (page 10, lines 12-21). At these and other places in the specification, including the data described in the working Examples the Examiner refers to in the Office Action, Applicants have affirmatively set forth the objective enablement of the claimed invention.

In order to make a rejection for lack of enablement, the Examiner bears the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. M.P.E.P. § 2164.04 (citing *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)). Thus, as the court stated in *In re Marzocchi*,

> it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure.

439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). Accordingly, Applicants' specification must be taken as enabling in the absence of objective evidence contradicting the truth or accuracy of specific assertions of enablement made in the specification. If the PTO cannot do so, Applicants respectfully submit that this 35 U.S.C. § 112, first paragraph rejection must be withdrawn.

Applicants respectfully submit that the PTO has failed to present a *prima facie* case of lack of enablement of the claims here, and that Applicants' specification must therefore be deemed enabled, because no objective evidence concerning Applicants' claimed invention has been presented. Instead, the PTO has merely discussed the alleged scope of the claims without

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elected Group I (Office Action at page 2).

indicating why the claims are not enabled. Both the techniques for practicing the invention and the techniques for testing whether or not p53 transactivating activity is restored are described in the specification, as noted above. Applicants have indeed enabled the claimed invention to one of ordinary skill in the art.

Furthermore, there simply is no reason in law or logic for requiring Applicants to demonstrate that every possible single-chain antibody works as disclosed here for preventing hyperproliferation in every possible cell. Satisfaction of the enablement requirement does not turn solely on the presence or absence of working examples for every conceivable embodiment. Indeed, the specification need not contain any example at all if the invention is otherwise disclosed in such a manner that one skilled in the art will be able to practice it without undue experimentation. *In re Borkowski*, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970). The Examiner has failed to explain why Applicants' disclosure, including several working examples, does not enable the invention. Nor has the Examiner provided any objective evidence suggesting that any of Applicants' assertions of enablement, Examples, or other disclosures are untruthful or inaccurate.

For the foregoing reasons, Applicants therefore respectfully request withdrawal of this rejection.

The Rejection of Claim 47 For Failure To Teach How To Make And/Or Use The Invention Should Be Withdrawn Because The Examiner Has Applied The Wrong Standard For Enablement

The Examiner rejected claim 47 under 35 U.S.C. § 112, first paragraph, as non-enabling for allegedly failing to teach one of ordinary skill "how to make and/or use" the invention. The Examiner recognizes that the specification teaches (1) nucleotide sequences encoding single-chain antibodies that bind to p53 mutants; (2) that these single-chain antibodies restore the function of inactive mutant p53 protein; (3) the lipofectamine mediated transfection of a plasmid

vector encoding these single-chain antibodies into tumor cells; (4) the expression of the gene product in tumor cells; and (5) that the transfected tumor cells exhibit increased mutant p53 transcriptional activity in-vitro (Office Action at pages 3-4). Nonetheless, the Examiner rejects claim 47, directed to a method of treating a hyperproliferative disorder involving a mutated p53 protein, because the specification fails to disclose every single-chain antibody that binds to all p53 mutants to restore p53 transactivation; because it does not disclose the restoration of p53 transactivation in any cell in vivo using any and all vectors; and because it does not disclose the treatment of all hyperproliferative disorders involving any and all p53 mutants, by administering a nucleic acid encoding single-chain antibodies which bind to all p53 mutants (Office Action at page 4).

As noted above, there simply is no reason in law or logic for requiring Applicants to demonstrate that every possible single-chain antibody works as disclosed here for preventing hyperproliferation in every possible cell. Satisfaction of the enablement requirement does not turn solely on the presence or absence of working examples for every conceivable embodiment. Indeed, the specification need not contain any example at all if the invention is otherwise disclosed in such a manner that one skilled in the art will be able to practice it without undue experimentation. *In re Borkowski*, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970). Applicants' specification discloses examples in which different tumor cell lines (H358, H1299, and HT29) were transfected with nucleic acid encoding single-chain antibodies and showed the restoration of p53 transcriptional activity (see, for example, Example 8 at page 39, line 24 to page 40, line 20). Moreover, as discussed above, Applicants' specification provides detailed information describing how to isolate the single-chain antibodies that bind p53 mutants; how to construct the various kinds of vectors; and how to introduce the single-chain antibodies into the

cell to effect the desired response (*see, e.g.*, pages 25-40, Examples 1-8). The Examiner has provided no objective evidence suggesting that any of Applicants' assertions of enablement, Examples, or other disclosures are untruthful or inaccurate.

The Examiner requires Applicants to satisfy a standard that is both impossible to meet and contrary to law – essentially requiring Applicants to, *inter alia*, provide working examples demonstrating every possible single-chain antibody that binds every possible p53 mutant, in every possible cell, using every possible vector, to treat every possible hyperproliferative disease caused by p53 mutation (Office Action at 4). In support of this standard, the Examiner cites a number of articles describing the uncertain nature of cancer gene therapy and the clinical challenges such treatments have presented. Applicants respectfully submit that the Examiner's reliance on the state of the art of cancer gene therapy in a clinical setting is misplaced. The cited articles merely demonstrate the absence of satisfactory clinical results in using gene therapy to cure cancer. It is improper under the PTO's own rules to predicate an enablement rejection on the absence of demonstrated level of effectiveness in a clinical setting. *See* M.P.E.P. § 2107.02 ("While an applicant may on occasion need to provide evidence to show that an invention will work as claimed, it is improper for Office Personnel to request evidence to request evidence of safety in the treatment of humans, or regarding the degree of effectiveness" (citations omitted)).

The Examiner's reliance on the unpredictability of cancer gene therapy and the existence of multiple factors contributing to the activity of cancer cells is similarly misplaced. The Examiner recites a litany of experiments that one would allegedly have to conduct in order to practice the invention to "elicit the claimed therapeutic effects." These experiments would include making and characterizing "any and all" single-chain antibodies binding to "any and all" p53 mutants, and making "any and all" vectors encoding the characterized single-chain

antibodies (Office Action at page 6). To the contrary, Applicants have fully enabled one of ordinary skill in the art to introduce a nucleic acid encoding a single-chain antibody which binds mutated p53 protein and has shown that these single-chain antibodies are expressed to restore p53 transactivation activity.

As discussed above, to sustain a lack of enablement rejection, the PTO must present objective evidence contradicting the truth or accuracy of Applicants' assertions that the invention is enabled in vivo. *In re Marzocchi*, 169 USPQ 367, 370 (CCPA 1971). The examiner has not set forth any evidence suggesting that Applicants' statements that the invention can be used in vivo are untrue or inaccurate. Moreover, notwithstanding any alleged unpredictability of cancer treatments in general, it is has been shown that gene therapy directed to activating p53 protein is therapeutically effective in vivo. *See, e.g.*, Roth, *et al., Retrovirus-Mediated Wild-Type p53 Gene Transfer to Tumors of Patients With Lung Cancer*, Nature Medicine, Vol. 2:985 (1996). Thus, one of ordinary skill in the art would not only be enabled to make and use Applicants' invention from the disclosure in the specification, but also would expect that the method would be useful in treating hyperproliferative disorders involving mutated p53. Accordingly, Applicants respectfully request withdrawal of the rejection of claim 47.

For all of the above reasons, Applicants respectfully request withdrawal of the Examiner's rejections of claims 28-39, 43-44 and 47 under 35 U.S.C. § 112, first paragraph.

The Jannot, *et al.* Reference Cited By The Examiner Does Not Teach All Of The Elements Of The Claimed Invention, And Therefore Cannot Anticipate Applicants' Invention

The Examiner rejects claims 28-31, 33 and 39 under 35 U.S.C. § 102(a) as being anticipated by Jannot, *et al.* (Biochem. Biophys. Res. Com. 230:242-246 (1997)). Applicants respectfully traverse this rejection.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). In support of this anticipation rejection, the Examiner notes that Jannot, *et al.* discuss that the injection of Pab421 antibody into cells restores the p53 transactivation activity of a p53 mutant (Office Action at page 7 and Jannot *et al.* at page 245, col. 1). Nowhere do Jannot, *et al.* discuss a single-chain antibody in a cell having a mutant p53 protein. The rejected claims are directed to the introduction of single-chain antibodies that bind mutated p53. Jannot, *et al.* do not teach single-chain antibodies that bind mutated p53. Rather, their disclosure discusses single-chain antibodies that bind fragments of wild-type p53 protein (*see, e.g.*, Jannot, *et al.*, at 242, col. 2, para. 3). Accordingly, a single-chain antibody that binds mutated p53 is missing entirely from the Jannot, *et al.* reference. Applicants therefore respectfully submit that the Examiner's rejection of claims 28-31, 33 and 39 should be withdrawn.

Conclusion

In view of the remarks above, Applicants request reconsideration and timely notice of allowance. If the Examiner believes that prosecution might be furthered by discussing the application with Applicants' representatives, in person or by telephone, we would welcome the opportunity to do so.

Applicants have provided for a three-month extension above. No additional extension of time fees, requests for extension of time, petitions, or additional claim fees are believed to be necessary to enter and consider this paper. If, however, any extensions of time are required or any fees are due in order to enter or consider this paper or consider any paper accompanying this paper, including fees for net addition of claims, applicants hereby request any extensions or

petitions necessary and the Commissioner is hereby authorized to charge our Deposit Account No. 50-1129 for any fees. If there is any variance between the fee submitted and any fee required, including the extension of time fee and fee for net addition of claims, the Commissioner is hereby authorized to charge or credit Deposit Account No. 50-1129.

Respectfully submitted,

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